510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

K050043

B. Purpose for Submission:

To add a revised (Erythromycin) antimicrobial formulation to the Dried Gram-Positive MIC/Combo Panels

C. Measurand:

Erythromycin at concentrations of 0.25-16 mcg/ml

D. Type of Test:

Quantitative and Qualitative growth based detection

E. Applicant:

Dade Behring
Dade MicroScan Inc.

F. Proprietary and Established Names:

MicroScan® Dried Gram-Positive MIC/Combo Panels

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   Class II

3. Product code:
   LRG-Instrument for Auto Reader & Interpretation of Overnight Antimicrobial Susceptibility Systems
   JWY - Manual Antimicrobial Susceptibility Test Systems
   LTT – Panels, Test, Susceptibility, Antimicrobial

LTW – Susceptibility Test Cards, Antimicrobial

4. Panel:
   83 Microbiology

H. Intended Use:

1. Intended use(s):

   For use with MicroScan® Dried Gram Positive MIC/Combo, Dried Gram Positive Breakpoint Combo and Dried Gram Positive ID Type 2 panels. MicroScan® Positive panels are designed for use in determining antimicrobial agent susceptibility and/or identification to the species level of rapidly growing aerobic and facultatively gram-positive cocci, some fastidious aerobic gram positive cocci and *Listeria monocytogenes*. Refer to Limitation of Procedure Section for use with fastidious streptococci.

2. Indication(s) for use:

   The MicroScan® Dried Gram-Positive MIC/Combo Panel is used to determine quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative anaerobic gram positive cocci. This indication is for the addition of the antimicrobial erythromycin at concentrations of 0.25 to 16 ug/mL to the test panel.

3. Special conditions for use statement(s):
   The Prompt® method of inoculation is an alternate method of inoculation preparation that is supported in the methodology along with the turbidity method. The stationary and log inoculum methods should not be used with this antibiotic.

   Results should not be reported for *Listeria monocytogenes.*

4. Special instrument requirements:

   These panels can be read at $\geq$ 16 hours of incubation either manually, automatically on the autoScan® 4, or with the WalkAway® instrument systems.

I. Device Description:

The MicroScan® Dried Gram-Positive MIC/Combo Panel contains microdilutions of each antimicrobial agent in various concentrations with Mueller Hinton Broth and various nutrients which are dehydrated and dried in panels. Each panel contains two control wells: a no-growth control well (contains water only/no nutrients or broth), and a growth control well (contains test medium without antibiotic). The panel is rehydrated and inoculated at the same time with 0.1 ml of suspension prepared by the turbidity method (inoculum prepared in water, then 0.1ml transferred to 25ml of inoculum water containing pluronic-D/F-a wetting solution) for a final inoculum of 3-

7 X 10^5. The Prompt® method of inoculation is also recommended as an alternate means of preparing the inoculum. The panels are incubated at 35^o C in a non-CO_2 incubator for 16-20 hours and read by visual observation of growth. Panels may also be read automatically with the WalkAway® or the AutoScan®4.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   MicroScan Dried Gram-Positive and Gram-Negative MIC/Combo Panels

2. Predicate 510(k) number(s):

   k862140

3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
Intended Use	See above	Same
Inoculum preparation	Inoculum prepared from isolated colonies using either the Turbidity method or Prompt® system	Same
Technology	Growth based after 16 hours incubation	Same
Results	Report results as minimum inhibitory concentration (MIC) and categorical interpretation (SIR)	Same
Instrument	autoScan® -4 or WalkAway®	Same
Differences		
Item	**Device**	**Predicate**
Antibiotic	Erythromycin at 0.25-16ug/mL	Different concentrations depending on the antibiotic
Test organism	*Staphylococcus aureus, Enterococcus faecalis Beta hemolytic Streptococci*	Varies according to the antibiotic
Limitations	Do not report *Listeria monocytogenes.*	Varies according to the antibiotic

K. Standard/Guidance Document Referenced (if applicable):

Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test

(AST) Systems; Guidance for Industry and FDA"; (CLSI) Clinical and Laboratory Standards Institute M7 (M100-S15) "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard".

L. Test Principle:

After incubation in a non-CO_2 incubator for 16-20 hours, the minimum inhibitory concentration (MIC) for the test organisms are read by determining the lowest antimicrobial concentration showing inhibition of growth. The panels are read either manually using a touchScan® SR, or with the autoScan 4® or the WalkAway® instrument, which uses an optics systems with growth algorithms to directly measure organism growth.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:
Reproducibility was demonstrated using 10 isolates tested at 3 sites on 3 separate days in triplicate. All ten isolates had a mode that was on scale. The mode was determined by the method used and therefore is not always the same for each method. The study included the testing of the following inoculum and reading variables; turbidity inoculum method and Prompt® method of inoculation with reading performed manually using a touchScan SR, autoScan 4® or the WalkAway® instrument. The following table provides the overall results for all combinations of these variables

Difference in the number of dilutions between the mode of the MicroScan result and the actual result with each different variable for between site reproducibility						
Inoculation method	Read method	≥ Minus 2 dilutions	Minus 1 dilution	Exact	Plus 1 dilution	≥ Plus 2 dilutions
Turbidity	Manual	4	64	202	5	0
Turbidity	WalkAway ®	1	46	191	35	1
Turbidity	autoScan® 4	2	57	189	21	1
Prompt®	Manual	2	37	187	47	2
Prompt®	WalkAway ®	3	26	226	18	1
Prompt®	autoScan® 4	5	27	188	47	4

The data demonstrates that there is good reproducibility of each method but since the modes of each are used and they may not be the same, this does not demonstrate if there is a difference between methods. The actual data points and the modes did demonstrate that when there was a difference the Prompt® method of inoculation was more resistant if only by one well. This was more apparent in the Staphylococcus isolates. These were the same isolates that were used in the colony count inoculum density study which did demonstrate a higher CFU for the staphylococcus which would explain the trend here.

b. *Linearity/assay reportable range:*

Not Applicable

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Quality Control was performed daily with the turbidity method and with the Prompt® selectively with the following results. The expected ranges are listed in the table and are also included in the final package insert.

Organism	Reference Conc. In ug/mL	Reference result	Micro Conc. tested	Turbidity inoculation with Read methods			Prompt® inoculation with Read methods		
				Manual	Walk-Away®	Auto-Scan®	Manual	Walk-Away®	Auto-Scan®
S. aureus ATCC 29213 Expected range 0.25-1 ug/mL	≤0.016								
	0.03								
	0.06								
	0.12	1							
	0.25	79	≤0.25	98	76	73	56	56	54
	0.5	6	0.5	9		2	50	19	21
	1	1	1	2	1	1			
	2		2						
	4		4						
	8		8						
	16		16						
	>16			1					
E. faecalis ATCC 29212 Expected range 1-4 ug/mL	≤0.016								
	0.03								
	0.06								
	0.12								
	0.25		≤0.25						
	0.5		0.5						
	1	6	1	9	19	13	8	8	8
	2	80	2	99	57	63	99	69	68
	4	1	4	1			2		
	8		8						
	16		16						
	>16		>16	1	1				

The difference in the staphylococci manual turbidity readings and the manual Prompt® reading results demonstrated the same effect observed in the reproducibility where there was a difference of one well more resistance for the Prompt® method of inoculation and even more pronounced with the Prompt® method of inoculation and the manual readings. This would be

expected since the Prompt® method of inoculation often produces a higher CFU/ml in the final panel.

Inoculum density control: A turbidity meter was used for the turbidity inoculation method with daily checks. The Prompt® method of inoculation had colony counts performed periodically throughout the study to determine the average inoculum density since there is no visual check of the inoculum using this device. The Prompt® method of inoculation had far more variability with average inoculum ranges from $5.08x10^5$-$1.8x\ 10^6$ with an actual data point range of 3.7×10^4 to 5.9×10^6. The inoculum of the Prompt® method of inoculation generally provides a higher number of CFU with more variability than a method using a turbidity meter as demonstrated in this study. The average of the staphylococcus tested was outside the recommended range for the CLSI reference method. The user is referred to the limitation section for the recommendations of when to use an alternate method.

The firm conducted a Pluronic F validation study to authenticate the use of Pluronic to inoculate frozen reference panels. When MICs from frozen reference panels inoculated with water were compared to panels inoculated with water and Pluronic, the essential agreement was acceptable.

d. Detection limit:

Not Applicable

e. Analytical specificity:

Not Applicable

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:
Clinical testing was performed at three sites using fresh isolates supplemented with stock isolates. A comparison of the MicroScan® Dried Gram-Positive test panel results was made to the reference method conducted as recommended in the CLSI standard M7-A6 except for the Pluronic F inoculum water. Testing of the reference method and the MicroScan® panels was performed at the same time. A challenge set was also tested at one site and compared to the reference broth dilution result mode that was determined by previous testing of each isolate multiple times in the recommended reference panel. *Staphylococcus spp.*, beta hemolytic streptococcus and

Enterococcus spp. were considered in the evaluation. All isolates tested grew in the MicroScan® panels.

	total	EA	%EA	Total evaluable	EA of evaluable	%EA	CA	%CA	#R	min	maj	vmj
Clinical	395	378	95.7	56	47	83.9	373	94.4	196	15	6	1
Challenge	128	125	97.7	10	8	80.0	126	98.4	35	1	0	1
Combined	523	503	96.2	66	55	83.3	499	95.4	231	16	6	2

EA-Essential Agreement
CA-Category Agreement
R-resistant isolates
maj-major discrepancies
vmj-very major discrepancies
min- minor discrepancies

Evaluable results are those that fall within the test range of the reference method and could also be on-scale with the new device if within the plus/minus one well variability. EA is when there is agreement between the reference method and the MicroScan® within plus or minus one serial two-fold dilution of antibiotic. CA is when the interpretation of the reference method agrees exactly with the interpretation of the MicroScan® result.

The challenge set of organisms was also tested using the Prompt® method of inoculation with all reading methods and the turbidity method of inoculation with the WalkAway® and the autoScan®4. This included one hundred thirty four challenge isolates that were tested at one site. The inoculum was prepared by the turbidity or Prompt® method and incubated in the WalkAway® instrument. All panels had additional readings performed after the WalkAway® reading was completed using the autoScan®-4 and then manually on the touchSCAN®-SR. The table below demonstrates the numbers that were in exact agreement with the reference method result and those that differed by one or more wells.

Difference in the number of dilutions between the expected reference result and the MicroScan® Result						
Inoculation method	Read method	$\leq$ minus 2 dilutions	minus 1 dilution	Exact	Plus 1 dilution	$\geq$ Plus 2 dilutions
Turbidity	Manual	13	16	61	1	9
Turbidity	WalkAway ®	13	16	61	1	10
Turbidity	autoScan® 4	13	16	61	1	10
Prompt®	Manual	13	16	61	1	9
Prompt®	WalkAway ®	13	16	61	1	9
Prompt®	autoScan® 4	13	16	61	1	9

All methods were of $\geq$ 90 % essential agreement.

b. Matrix comparison:

Not Applicable

3. Clinical studies:

   a. Clinical Sensitivity:

   Not Applicable

   b. Clinical specificity:

   Not Applicable

   c. Other clinical supportive data (when a. and b. are not applicable):

   Not Applicable

4. Clinical cut-off:

   Not Applicable

5. Expected values/Reference range:

   ≤ 0.5 (S), 1-4 (I), ≥ 8 (R) for *Staphylococcus spp*. and *Enterococcus spp.*

   ≤0.25 (S), 0.5 (I), >1 (R) for Beta hemolytic Streptococcus

   The interpretative criteria and Quality Control Ranges are the same as recommended in the FDA approved pharmaceutical package insert and the CLSI. All values are included in the package insert.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.